GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Antigastric ulcer activity of *Ludwigia octovalvis* (Jacq.) P. H. Raven (ONAGRACEAE) hydroalcoholic extract

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GSC Biological and Pharmaceutical Sciences, 2022, 21(03), 077–081

Publication history: Received on 30 October 2022; revised on 04 Decemeber 2022; accepted on 07 December 2022

Article DOI: https://doi.org/10.30574/gscbps.2022.21.3.0463

Abstract

Ludwigia octovalvis is used to treat stomachache in Malagasy traditional medicine. The present study was carried out to evaluate the anti-ulcer activity of its hydroalcoholic leaf extract in rats. Pylorus ligation and indomethacin-induced models were used to evaluate its anti-secretory and mucoprotective activities. Cimetidine (100 mg/kg) and Misoprostol (1.43 µg/kg) were used as the standard drugs. The extract was administered orally at doses 150, 300 and 600 mg/kg. The extract exhibited significant ulcer inhibition in indomethacin-induced ulcer model. The lesion surface area of the control group mucosa is equal to 6.2 ± 0.50 mm^2, versus 4.32 ± 0.1, 2.75 ± 0.10 and 1.12 ± 0.05 mm^2 in rat treated with the extract, and 2.1 ± 0.1 mm^2 for the rats treated with misoprostol ($p<0.05$). It also reduces the gastric content acidity, which is equal to 2.79 ± 0.1 in control group, to 3.13 ± 0.1, 3.25 ± 0.2 and 5.31 ± 0.2 in the animals treated with the extract and 5.79± 0.1 for the animals treated with cimetidine ($p<0.05$). The extract showed significant reduction in mucosa lesion surface area and gastric content acidity, dose dependent compared to control.

Keywords: *Ludwigia octovalis*; Anti-secretory; mucoprotective; Anti-ulcer; Rat

1 Introduction

Gastric ulcer is a disruption in the integrity of gastric mucosa that extends to sub mucosa or deeper into the muscularis. It is the consequence of lack of equilibrium between the gastric aggressive factors (acid, pepsin, H. pylori and aggressive agents or medications) and the mucosal defensive factors (mucus, bicarbonate, blood flow and prostaglandins) [1]. Acetylcholine, gastrin, and histamine are the three major mediators responsible for gastric acid secretion. Acetylcholine, released by sympathetic stimulation, acts on M_3 muscarinic receptor on parietal cell to stimulate gastric acid secretion. This neuro mediator is also responsible for the gastrin secretion. This gastric hormone then stimulates the cholecystokinin-B receptor on the enterochromaffin-like cell, which releases histamine. Fixation of histamine with H_2-receptor in the parietal cell results in activation of the gastric H^+/K^+ - ATPase enhances acid secretion. Gastric acid then activates pepsinogen into pepsin responsible of auto digestion of the inner gastric lining [2, 3]. Certain medications such as non-steroidal anti-inflammatory are also capable of gastric ulcer enhancement. These drugs inhibit the activity of cyclo-oxygenase (COX) in gastric mucosa. This reduces synthesis of prostaglandins responsible for the secretion mucus and bicarbonate, and the mucosal blood flow [4].

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The incidence of peptic ulcer disease (PUD) varies with age, gender, geographical location and is associated with severe complications including hemorrhages, perforations, gastrointestinal obstruction, and malignancy. Thus, it represents a worldwide health problem because of its high morbidity, mortality and economic loss.

The aims of ulcer disease treatment are to relieve pain, heal the ulcer and delay its recurrence. It is based on reducing acid output or increasing mucosal protection [5]. Numerous natural products have been evaluated as therapeutics for peptic ulcer. This article will be concerned only with the antiacid secretory and mucosal-protective effects. Therefore, the aim of this study was to determine the anti-ulcerogenic potential of the leaf extracts of *Ludwigia octovalvis* in rat model using pylorus ligation and indomethacin -induced ulcer.

2 Material and methods

2.1 Extraction

The leaves of *Ludwigia octovalvis* were collected from the northern part of Madagascar in May 2021. They were dried under shade and ground with an electric grinder. The powder was macerated in a mixture of ethanol and water (60:40) for 72 hours. The macerate was filtered and evaporated to dryness under vacuum with a rotavapor (Evapotec®). The dry extract was used for the biological tests.

2.2 Phytochemical screening

The hydroalcoholic extract was assessed for secondary metabolites using the methods described by Fong *et al.* [6]. This test is based on reaction between specific reagents and the corresponding family. The reaction is characterized by precipitate formation or changing coloration.

2.3 Animals of experimentation

Albino rats, Wistar strain, of both sexes, aged 3 to 4 months, weighing 200 to 250 g were used during the experiments. The animals were bred in the animal house of the Laboratoire de Pharmacologie Générale, de Pharmacocinétique et de Cosmétologie of the Faculty of Sciences, University of Antananarivo at a temperature of 22 ± 2 °C and kept under 12h/12h light/dark cycle. Rats were deprived of food but had free access to water 18 h prior to tests.

2.4 Evaluation of *Ludwigia octovalvis* extract effect on pylorus ligation induced gastric ulcer

Animals were fasted for 18 h before the start of the study but had free access to water. They were divided into 5 groups of 6 rats: the first one has served as control group, the second as positive control, and three groups were treated with the extract at the doses of 150, 300 and 600 mg/kg, by oral route, in a maximal volume of 10 ml/kg. The animals of control group received distilled water, those of the second group received 100 mg/kg of cimetidine, and the animals of the three groups received the extract [7]. After 30 minutes of drug treatment, they were anesthetized with ether and the abdomen was opened by a small midline incision below the xiphoid process. Pylorus was slightly lifted out, with caution to avoid traction to the pylorus or damage to its blood supply, and ligated. The stomach was placed back to its position and the abdominal wall was closed by interrupted sutures. The animals were put in individual cages for 6 h, during which they were deprived of food. After 6 h of the pyloric ligation they were euthanized using phenobarbital 100 mg/kg i.m, and their carotids were cut. The abdomen was opened, cardiac end of the stomach was dissected out, and the contents were drained into glass tubes and centrifuged at 3000 rpm for 10 minutes. The supernatants were collected and their pH were measured [8].

2.5 Evaluation of *Ludwigia octovalvis* extract effect on indomethacin-induced gastric ulcer

The mucoprotective action of the extract was evaluated on its capacity to protect the animals from indomethacin-induced gastric lesions. Animals were fasted 18 h, and divided into 5 groups: 1 control group, 1 positive control group, and 3 treated with the extract at doses 150, 300 and 600 mg/kg. Every morning, at the same time, animals of the control group received distilled water, those of positive group received 1.43 µg/kg of misoprostol, and the rest received the extract. All the products were administered orally in a maximum volume of 10 ml/kg [7]. After 30 minutes, the animals of the 5 groups received 40 mg/kg of indomethacin daily for 5 days. On the 6th day, the animals were euthanized, using 100 mg/kg of phenobarbital i.m., and their carotids were cut. The stomachs were isolated, and cut open along the greater curvature, rinsed with normal saline solution to remove gastric contents and blood clots, and examined by a 10X magnifier lens. The surface area of lesions on gastric wall was measured by direct planimetry, using transparent millimetric paper [9].

2.6 Results expression and statistical analysis

Results are expressed as mean ± standard error of the mean (SEM). Statistical significance was determined by one way analysis of variance (ANOVA) followed by Student's 't' test, p-value less than 0.05 was considered statistically significant. The data were then presented using figures.

3 Results

3.1 Phytochemical screening

Preliminary phytochemical screening of *Ludwigia octovalvis* confirmed the presence of different secondary metabolites, such as flavonoids, tannins, polysaccharides, triterpenes, phenolic compounds, anthocyanins and saponins.

3.2 Anti-secretory activity of *Ludwigia octovalvis* extract

Administered orally at doses 150, 300 and 600 mg/kg, *Ludwigia octovalvis* extract reduces the gastric content acidity. It increases the pH value compared to the control group, and its effect is dose dependent and comparable to the standard drug cimetidine. The pH of the control group gastric content is equal to 2.79 ± 0.1, versus 3.13 ± 0.1, 3.64 ± 0.1 and 5.13 ± 0.10 for the animals treated with the extract and 5.79 ± 0.1 for the animals treated with the reference drug at 100 mg/kg ($p<0.05$) (Figure 1). These results indicate the anti-secretory activity of *Ludwigia octovalvis* hydro alcoholic extract.

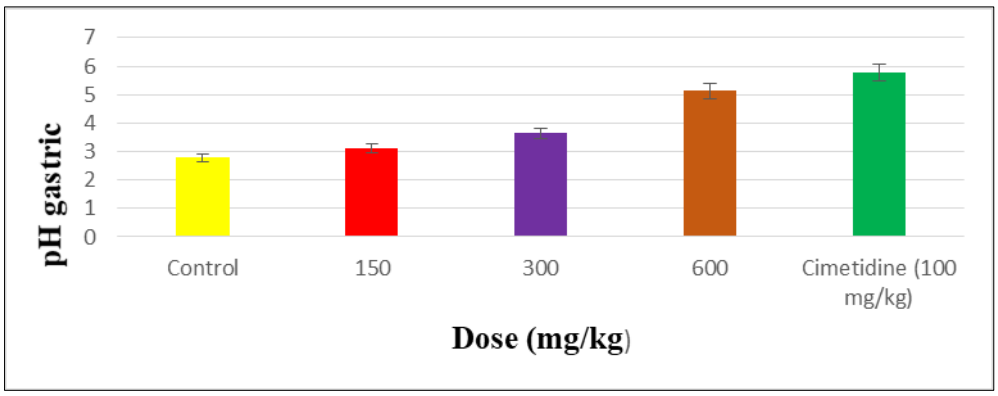

Figure 1 pH of gastric content of the animals in control group and treated with the extract at the doses of 150 , 300 and 600 mg/kg , and animals treated with cimetidine (100 mg/kg) , after pylorus ligation ($\bar{x} \pm \bar{\sigma}$; n= 6; $p<0.05$)

3.3 Mucoprotective activity of *Ludwigia octovalvis* extract

Administered orally at the dose of 40 mg/kg per day for 5 days, indomethacin provokes lesions on the gastric mucosa. But the surface area of mucosa lesion on gastric lining of animals treated with *Ludwigia octovalvis* extract at different doses are less than the lesion observed on gastric mucosa of the animals of control group. The lesion surface area reduction is dose dependent, and the results obtained with the doses 300 and 600 mg/kg are comparable to the reference drug, misoprostol at the dose 1.43µg/kg.

The lesion surface area for the control group is equal to 6.2 ± 0.50 mm^2, versus 4.32 ± 0.1, 2.75 ± 0.10 and 1.12 ± 0.05 mm^2 in the animals treated with the extract ($p<0.05$), and 2.1 ± 0.1 mm^2 for animals treated with the reference drug misoprostol at the dose of 1.43 µg/kg (Figure 2). These results exhibit the mucoprotective activity of *Ludwigia octovalvis* extract.

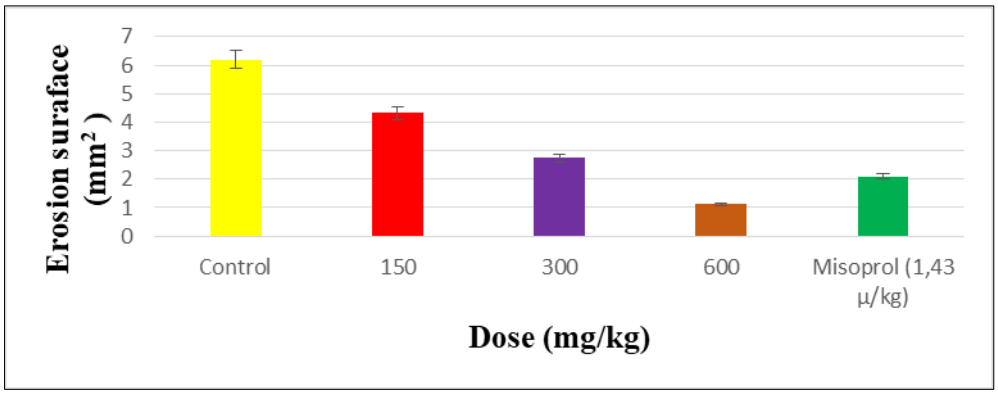

Figure 2 Surface area of induced indomethacin (40 mg/kg) gastric lesion of the animals in control group and those treated with the extract at the doses of 150, 300 and 600 mg/kg and the animals treated with misoprostol (1.43 µg/kg) ($\bar{x} \pm \bar{\sigma}$; n= 6; $p<0.05$)

4 Discussion

The decoction of the leaves of *Ludwigia octovalvis* is widely used in Malagasy traditional medicine to treat stomach-ache. Therapy for gastroduodenal ulcer is based on reducing acid secretion or increasing the mucosa protection. To authenticate the empirical use of this plant, we used two models: pylorus ligation-induced ulcer model and indomethacin-induced ulcer model. The effect of the hydro alcoholic extract on pH and ulcerations was evaluated.

Pylorus ligation stimulates the antral parasympathetic nerve, leading to acetylcholine release. The fixation of this neuro mediator fixes on M3 receptor of the parietal cells induces gastric acid secretion, followed by pepsinogen activation. This process increases accumulation of gastric acid and pepsin, leading to the auto-digestion of the gastric mucosa [10]. In the present study, *Ludwigia octovalvis* extract decreases the gastric content acidity significantly. It indicates the anti-secretory of the extract. This action might be due to the inhibition of the proton pump on the parietal cells. It is known that flavonoids block acid formation in parietal cells by inhibiting H^+/K^+ - ATPase [11]. From these findings, we suggest that because of the flavonoids that the extract contains, *Ludwigia octovalvis* hydro alcoholic extract could inhibit the enzyme H^+/K^+ ATPase. Hence it reduces the gastric acidity which is already a good point for an antiulcer drug.

On the other hand, the extract also reduces the lesion surface area on gastric lining induced by indomethacin. As a non-steroidal anti-inflammatory, this drug inhibits COX, leading to decrease of prostaglandins synthesis. Meanwhile those mediators are responsible for mucus and bicarbonate secretion in gastric mucosa. Lack of prostaglandins decreases the protective mechanism of the gastric lining. The results of the test that we have conducted indicate that *Ludwigia octovalvis* extract decreases the lesion surface area on gastric mucosa, which means it is capable of counteract the action of indomethacin. On top of its capacity to reduce the acid secretion, it might also be capable of increasing the protection of the gastric lining through mucus and bicarbonate secretion. The reduction of the ulcerated surface area suggests that the extract might increase the prostaglandins production. It is reported in literature that flavonoids are effective to stimulate PGE2 production in gastric mucosal cells [12]. Polysaccharides also protect against gastric ulcers [13].

Based on the results obtained, we can advance the hypothesis that *Ludwigia octovalvis* hydro alcoholic extract could be effective as an anti-gastric ulcer medication, since it is able to reduce the acidity and increase the protective mechanism of the gastric mucosa, and that its anti-ulcer activity might be due to the flavonoids and polysaccharides in it.

5 Conclusion

The results of the present study suggest that ulcer activity of *Ludwigia octovalvis* hydroalcoholic extract observed during the empiric use may be due to both gastric antisecretory and cytoprotective effects. From the present study, it can be concluded that *Ludwigia octovalvis* extract exhibited a promising anti-gastric ulcer activity on pyloric ligation, indomethacin-induced ulcer models and this finding supports the traditional-claimed-use of the leaf of *Ludwigia octovalvis* against stomach ache. Thus, it could be considered as a potential source to develop new anti-ulcer agents.

Compliance with ethical standards

Acknowledgments

The authors are sincerely acknowledged to the Laboratory LPGPC (Laboratoire de Pharmacologie Générale, Pharmacocinétique, Cosmétologie) for providing the necessary facilities to carry out the research project successfully.

Disclosure of conflict of interest

The authors declare no conflict of interests.

Statement of ethical approval

The experiments were conducted following the guidelines of the ethic committee of the Sciences Faculty, University of Antananarivo, Madagascar (Ref: 17/2021).

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